Optical isomers of N,N'-bis(1-phenylethyl)-2,6-pyridinedicarboxamide coordinated to europium(III) ions as reliable circularly polarized luminescence calibration standards†

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The synthesis of two optical isomers of N,N'-bis(1-phenylethyl)-2,6-pyridinedicarboxamide and the constant circularly polarized luminescence (CPL) activity of their acetonitrile trivalent europium complex solutions over a long period of time open new perspectives for performing accurate routine CPL calibration tests at low cost.

Generally speaking, circularly polarized luminescence (CPL) spectroscopy is the emission analog to circular dichroism (CD) spectroscopy. CD allows one to detect the differential absorption of left and right circularly polarized light, while CPL measures the difference in the emission intensity of left circularly polarized light *versus* right circularly polarized light. CPL has primarily been focused on studies aimed at investigating the chiral structures and solution dynamics of luminescent lanthanide complexes. A recent review has summarized the various types of applications of CPL aimed at getting quantitative and/or qualitative chiral structural information of selected systems that do not racemize on the emission timescale.[1] Some of the more important applications of CPL are briefly discussed below.

CPL is becoming increasingly useful as a probe for luminescent lanthanide complexes as sensory systems for anion binding in aqueous media or the existence of chiral lanthanide structures (*i.e.* to establish the predominant isomer in solution or if the solution of a complex containing an achiral ligand is indeed a racemic mixture), and as an indicator of changes in chiral structure (*i.e.* the importance of the helical wrapping of the ligand strand contribution and, therefore, the influence of this latter on the diastereomeric induction). In addition, information concerning metal-ion environments and the associated chiral structures of metal-containing biological systems can be obtained through the measurement of CPL.

It is common to report the degree of CPL in terms of the luminescence dissymmetry factor, $g_{lum}(\lambda)$, which is defined as follows: $g_{lum}(\lambda) = 2\Delta I/I = 2(I_L - I_R)/(I_L + I_R)$, where I_L and I_R refer, respectively to the intensity of left and right circularly polarized emissions. The transitions studied in CPL are generally the magnetic dipole allowed transitions that are electric dipole forbidden, where one predicts the CPL would be large. For Eu(III),

the $^5D_0 \rightarrow {}^7F_1$ transition is particularly well-suited for CPL measurements since it satisfies the magnetic-dipole selection rule, $\Delta J = 0, \pm 1$ (except $0 \leftrightarrow 0$), and therefore would be the transition to be considered for calibration purposes. It should be noted that a value of 0 for g_{lum} corresponds to no circular polarization, while the absolute maximum value is 2. For example, absolute g_{lum} values of 0.25 and 0.29 have been reported for Eu(III) complexes with chiral DOTA- (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and 2-hydroxyisophthalamide-based ligand derivatives.[2,3] It is often the case that rigid lanthanide systems exhibit large g_{lum} values, while racemic or other types of mixtures give g_{lum} values in the range of $\sim 10^{-2}$–10^{-3}.[1] As a result, an accurate determination of the sign and magnitude of the CPL signal needs to be accomplished.

Unlike CD, the measurement of CPL is mainly dependent on the use of home-built instruments that have been designed, developed and improved by a limited number of research groups around the world over the last three decades.[1,4–6] However, the growing interest in developing chiral luminescent probes, and in particular lanthanide-based systems, has recently resulted in the commercialization of the first CPL spectrometer.[7] Although most of the CPL studies published in the literature have been done with custom-made instruments operating in a differential photon-counting mode,[1] the detection of CPL can now be done with a high degree of sensitivity ($\sim$ 1 part in 10^4–10^5) and reliability, depending on the total light intensity. The availability of a relatively simple CPL standard would be a necessary etalon due to the absence of comparative results between the currently home-built instruments used and commercial spectrometers available. In addition, all CPL instruments need to be regularly tested and calibrated for the detection of small degrees of circular polarization in the total emitted light intensity accurately. To date, the commercially available (Aldrich) NMR shift reagent tris(3-trifluoroacetyl-(+)-camphorato)europium(III) in DMSO, Eu((+)-facam)$_3$, is used as a CPL standard,[1,8] even though Schippers in 1982 suggested that the use of this "system/DMSO as a CPL calibration standard is questionable".[4] The magnitude of Schippers' measured g_{lum} values (-0.25, -0.78, and $+0.072$ at 588.2, 595.2 and 613.5 nm) did not match those reported by Brittain[8] in 1976 (-0.84, -1.98, and $+0.30$). In 1999, Maupin also showed that the CPL activity of Eu(facam)$_3$ complexes in DMSO is relatively sensitive to the presence of small amounts of water.[9] In addition to the water sensitivity, the high cost of Eu((−)-facam)$_3$ with the other enantiomeric form of facam limits its use as an effective and reliable CPL standard for routine tests.

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In this communication, we report on the use of a more suitable CPL calibrating agent based on optical isomers of N,N'-bis(1-phenylethyl)-2,6-pyridinedicarboxamide (**1**) coordinated to europium(III) ions in a Eu : **1** ratio of 1 : 3. In particular, the simple preparation in high yield of these new optical isomers, (R,R)-**1** and (S,S)-**1**, and the constant CPL activity of their MeCN europium(III) complex solutions over a long period of time are interesting properties to be considered for performing routine CPL calibrations. The isomer (R,S)-**1** (or *meso*-**1**) has also been prepared as a control. It should be added that our ligand of interest is based on an analog of the N,N'-dibenzyl-2,6-pyridinedicarboxamide ligand,[10] where the dibenzyl substituents have been replaced by chiral phenylethyl groups.

The three diamide stereoisomers were synthesized (Scheme 1) from 2,6-pyridinedicarboxylic acid chloride with a slight excess of (S)-$(-)$, (R)-$(+)$, or $(\pm)$-(α)-methylbenzylamine (**2**) in a one-step procedure using modified Schotten–Baumann conditions[11] (see ESI†). In these conditions, a two-phase medium is provided by the organic solvent, CH_2Cl_2, and the aqueous base, sodium bicarbonate. Ligands (R,R)-**1** and (S,S)-**1** were obtained in 90% yield, while (R,S)-**1** was isolated in 28% yield and 97.8% purity after four recrystallizations, as confirmed by NMR.[12] The opposite optical rotation values of (R,R)-**1** and (S,S)-**1** ($-213.4°$ and $+213.6°$, respectively) confirm the chirality arising from the asymmetric carbons and the preparation of each enantiomeric form of **1**, while an optical rotation value of $-0.8°$ for (R,S)-**1** corroborates the synthesis of the *meso* ligand with high purity.

The Eu-containing complex solutions were prepared *in situ* from stock solutions of Eu(III), Eu(OTf)$_3$ (OTf = trifluoromethanesulfonate) and each optical isomer of **1** in MeCN. The Eu(III) concentration was 6.67×10^{-3} M and the Eu : **1** ratio was 1 : 5 to ensure complete formation of the tris complex. These experimental conditions were determined based on the identification of the various Eu-containing species using the $^5D_0 \leftarrow {}^7F_0$ excitation spectroscopy. For instance, the $^5D_0 \leftarrow {}^7F_0$ excitation spectra of Eu–(R,R)-**1** solutions at various Eu : **1** ratios confirm the successive formation of 1 : n (n = 1–3) species (Fig. 1). At the lowest Eu : **1** ratio, the 1 : 1 complex (579.2 nm) is the major complex in solution; the other species in solution is the 1 : 2 complex (579.8 nm) while a third species corresponding to the tris complex (580.4 nm) is observed at higher ligand concentration. Finally, the high resolution excitation spectra show that the Eu(III) ions are in the form of the 1 : 3 species in a 6.67×10^{-3} M MeCN solution with a stoichiometric 1 : 5 ratio.[13] It should be noted that **1** forms stable tris complexes, as demonstrated by the measurement of a constant CPL activity over an extended period, and the observation of only two components for the $^5D_0 \rightarrow {}^7F_1$ transition is compatible with trigonal symmetry of the complex. A complete study of the stability, structural, chiroptical and photophysical properties of these compounds of interest will be described in a forthcoming publication. Furthermore, our solution stability
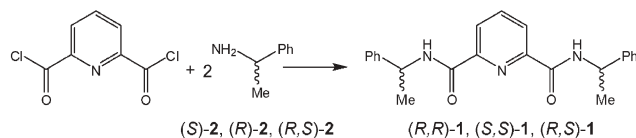
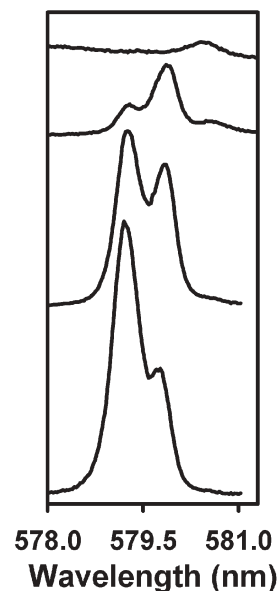**Fig. 1** $^5D_0 \leftarrow {}^7F_0$ excitation spectra of the Eu–(R,R)-**1** solutions at various Eu : **1** ratios (1 : 1, 1 : 2, 1 : 3 and 1 : 5 from bottom to top) in MeCN at 295 K. The Eu(III) concentration was 6.67×10^{-3} M. The luminescence was monitored at 615.6 nm.

results are consistent with those published by Le Borgne *et al.*[10] The authors showed the slow formation of stable triple-helical complexes with the N,N'-dibenzyl-2,6-pyridinedicarboxamide ligand (solutions equilibrated for one week), and also that the existence of several inert conformational isomers, due to the blocked rotations around the OC–N bonds, prevents complete characterization in solution. The slow complexation processes are due to the stabilization of this ligand in its *syn,syn,Z,Z* conformation.

The CPL spectra for the $^5D_0 \rightarrow {}^7F_1$, $^7F_2$, and $^7F_4$ transitions of each of the complex solutions with a Eu : **1** ratio of 1 : 5[13] were measured following excitation at 308 nm in MeCN at 295 K. As shown in Fig. 2, the detection of a CPL signal confirms the presence of stable chiral emitting species on the luminescence timescale. In addition, the observation of mirror image CPL spectra for the Eu(III) complexes with both enantiomers, (R,R)-**1** and (S,S)-**1**, shows that the emitted light is polarized in a direction determined by the helicity of the Eu(III) ion, which in turn is controlled by the absolute configuration at the carbon centers in the amide substituents. This result is also corroborated by the absence of detectable CPL activity for the Eu(III) compound with (R,S)-**1**. The CPL results are summarized in Table 1.

The most important feature of these systems is the stability of their complex solutions resulting in a CPL activity independent of the "age" of the solution. For instance, the g_{lum} values amounted to -0.18 and -0.18 at 595.3 nm ($^5D_0 \rightarrow {}^7F_1$) for a 1 : 5 Eu–$(R,R)$-**1** solution left on the shelf and measured seven months apart. In addition, these solutions have been exposed to a series of UV excitations (λ_{exc} = 308 nm) for several consecutive days without showing photochemical degradation.

In conclusion, we present here new Eu-containing compounds that can be used for performing accurate routine CPL tests at low cost. The advantages of these systems are (i) the ease of the synthesis of the optical isomers of **1**, which can be performed by

(S)-**2**, (R)-**2**, (R,S)-**2** $\longrightarrow$ (R,R)-**1**, (S,S)-**1**, (R,S)-**1**

Scheme 1
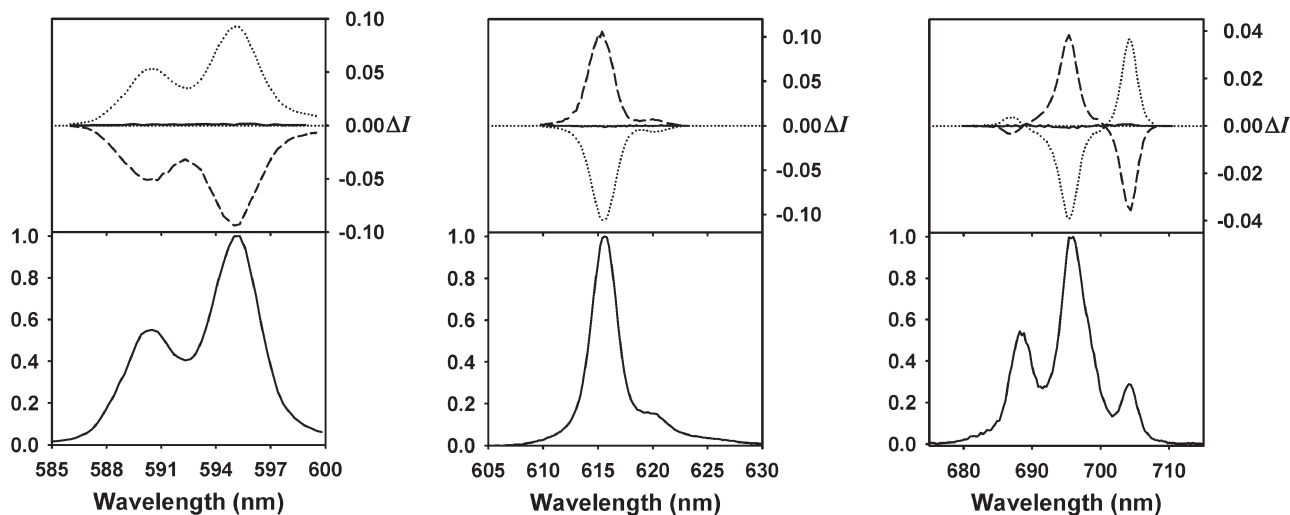
Fig. 2 Circularly polarized luminescence (upper curves) and total luminescence (lower curves) spectra of the Eu-containing compounds in a Eu : **1** ratio of 1 : 5 with the three optical isomers of N,N'-bis(1-phenylethyl)-2,6-pyridinedicarboxamide, (R,R)-**1** (dashed lines), (S,S)-**1** (dotted lines), and (R,S)-**1** (solid lines), in 6.67×10^{-3} M MeCN at 295 K, following excitation at 308 nm. Left: $^5D_0 \rightarrow {}^7F_1$ transition; middle: $^5D_0 \rightarrow {}^7F_2$ transition; right: $^5D_0 \rightarrow {}^7F_4$ transition.

Table 1 Summary of CPL results for the Eu-containing compounds in a Eu : **1** ratio of 1 : 5 with the two optical isomers of N,N'-bis(1-phenylethyl)-2,6-pyridinedicarboxamide, (R,R)-**1** and (S,S)-**1** in 6.67×10^{-3} M MeCN at 295 K, following excitation at 308 nm

Electronic transition	Wavelength/nm	$g_{lum} \pm \sigma_d{}^a$	
		(R,R)-**1**	(S,S)-**1**
$^5D_0 \rightarrow {}^7F_1$	590.5	-0.19 ± 0.01	$+0.19 \pm 0.01$
	595.3	-0.18 ± 0.01	$+0.18 \pm 0.01$
$^5D_0 \rightarrow {}^7F_2$	615.6	$+0.21 \pm 0.01$	-0.21 ± 0.01
$^5D_0 \rightarrow {}^7F_3{}^b$	649.6	-0.22 ± 0.01	$+0.23 \pm 0.01$
$^5D_0 \rightarrow {}^7F_4$	688.8	$+0.001 \pm 0.01$	-0.001 ± 0.01
	696.0	$+0.07 \pm 0.01$	-0.07 ± 0.01
	704.1	-0.24 ± 0.01	$+0.25 \pm 0.01$

^{a} Values from Fig. 1 (see ESI for experimental procedure). ^{b} Very low emission that prevents recording of a complete CPL spectrum.

undergraduate students, (ii) their complex solution stability (*i.e.* several months), once they have reached their thermodynamic equilibrium, and (iii) the lack of noticeable photochemical degradation under continuous UV excitation (*i.e.* three days). The combination of these properties opens new perspectives for the design of lanthanide(III) complexes acting as probes for chiral recognition.

Notes and references

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12 ^1H NMR in C_6D_6 is useful for determining the ratio of (S,S)-**1** and/or (R,R)-**1** *versus* (R,S)-**1**: the former isomers exhibit a doublet at δ 1.26 ppm that is nicely resolved from (R,S)-**1** at δ 1.32 ppm.
13 Although the $^5D_0 \leftarrow {}^7F_0$ excitation study indicates that the 1 : 3 complex is probably the main species in solution at a 1 : 3.5 ratio, a 1 : 5 ratio has been used as a precaution. Preliminary results suggest that the g_{lum} value is not affected by the excess of ligand, once the 1 : 3 complex has been completely formed in solution (ratios going from 1 : 3.5 to 1 : 5).